J. Med. Toxicol. (2016) 12:142–144
DOI 10.1007/s13181-015-0529-1

POSITION STATEMENT

Safety Issues Regarding Prescription Opioids

American College of Medical Toxicology

Published online: 5 January 2016

Disclaimer

This position statement addresses several specific areas regarding prescription opioid safety: (a) acetaminophen-opioid combination products; (b) total daily opioid dosage; (c) abuse-deterrent opioids. Outpatient fentanyl use and the use of methadone as an analgesic are discussed in separate position statements.

The position of the American College of Medical Toxicology (ACMT) on each topic is as follows:

Acetaminophen-Opioid Combination Products

It is the position of ACMT that when prescribing opioids, a risk-benefit analysis for both acetaminophen toxicity and opioid misuse should direct the choice of a combination analgesic. An acetaminophen-free product should be considered for those at risk for supratherapeutic dosing to avoid acetaminophen hepatotoxicity. Overall, ACMT supports the decision of the FDA to limit the acetaminophen content in opioid combination products.

Total Daily Opioid Dosage

The risk of drug-related overdose increases with increased opioid dosing, and there is no threshold dividing "safe" from "toxic" dosing. It is the position of ACMT that providers always exercise caution when prescribing outpatient opioids, especially in doses that exceed 50 mg daily (in morphine equivalents), due to the increased risk for drug-related overdose or death.

Abuse-Deterrent Opioid Formulations

ACMT supports the development of tamper-resistant and abuse-deterrent formulations as part of a comprehensive program to decrease opioid misuse. However, deterrence of abuse does not equate to full prevention of abuse. ACMT recognizes that abuse-deterrent formulations may have a limited impact on addiction and death, because in most cases, substance misuse involves oral administration of the intact drug and injection accounts for a small percentage of misuse. In addition, the impact on non-oral misuse will be limited because users may defeat the abuse-deterrent or tamper-resistant mechanism or shift to other legal or illicit opioid formulations, such as heroin.

While individual practitioners may differ, these are the positions of the ACMT at the time written, after a review of the issue and pertinent literature.

Background

The USA and Canada have witnessed a dramatic rise in the use of prescription opioids, especially in the treatment of non-cancer chronic pain [1–3]. This trend is particularly notable, as it has not been accompanied by a proportional increase in total physician encounters [1]. According to the United States Substance Abuse and Mental Health, 4.3 million Americans age 12 or older report current nonmedical use of prescription pain relievers [4]. The expanded use of prescription opioids has coincided with rising morbidity and mortality related to these medications [5]. The age-adjusted death rate attributable to prescription opioids increased fourfold from 1999 to 2009 [6]. In 2010, prescription opioids were involved in 75.2 % of US pharmaceutical overdose deaths [7]. The United States Centers for Disease Control and Prevention reported that, from 2011 to 2013, the heroin overdose death rate doubled

✉ American College of Medical Toxicology
positionstatements@acmt.net

[1] Phoenix, AZ, USA

in the USA. The same report showed that past-year use of opioid pain relievers was related to past-year heroin use or dependence [8]. Mortality rates show significant correlation with the total number of prescriptions for oxycodone, hydromorphone, and methadone, when data from individual US states are compared [9].

A. Acetaminophen-Opioid Combination Products

Acetaminophen remains the leading cause of acute liver failure in the USA [10, 11]. Oxycodone and hydrocodone are frequently prescribed as combination immediate-release formulations containing acetaminophen. Although malnutrition and glutathione-depleted states are risk factors for acetaminophen hepatotoxicity, increased acetaminophen dose is the principle cause of hepatic injury [12, 13]. Patients who develop tolerance to an opioid analgesic may increase their analgesic consumption, concomitantly increasing acetaminophen exposure. One national study reported that acetaminophen-opioid combinations were related to 63 % of unintentional acetaminophen overdose cases producing acute liver failure [10]. Historically, most combination products contained 325 mg acetaminophen per tablet, so an individual would only need to take about 12 tablets in a 24-h period to reach the maximum adult daily dose of 4 g. In 2009, an FDA advisory panel voted in favor of eliminating of acetaminophen-opioid combination products as a means of decreasing risk of acetaminophen toxicity [14]. While the FDA did not ultimately recommend elimination of these products, in January 2011, the agency did request that the acetaminophen content of opioid combination products be limited to 325 mg per unit dose (tablet, capsule, etc.).

It is the position of ACMT that when prescribing opioids, a risk-benefit analysis for both acetaminophen toxicity and opioid misuse should direct the choice of a combination analgesic. An acetaminophen-free product should be considered for those at risk for supratherapeutic dosing to avoid acetaminophen hepatotoxicity. Overall, ACMT supports the decision of the FDA to limit the acetaminophen content in opioid combination products.

B. Total Daily Opioid Dose

Patients maintained on chronic opioid therapy may require an increasing dose over time due to the development of tolerance. However, recent studies have demonstrated an increased risk for morbidity and mortality with escalating dose even in tolerant individuals. One study of patients receiving treatment for chronic, non-cancer-related pain reported an increased risk of overdose in those receiving opioid doses greater than 50 mg daily (of morphine equivalents) compared to patients receiving less than 20 mg daily [15]. Patients receiving doses between 50 and 100 mg daily experienced a hazard ratio of 3.73 for overdose, while patients receiving greater than 100 mg had a hazard ratio of 8.87. A subsequent study reported similar findings, even when study outcome was limited to unintentional death due to opioid overdose [16]. Patients with chronic pain who receive doses between 50 and 100 mg daily (of morphine equivalents) had a hazard ratio of 4.63 for overdose death compared to patients receiving less than 20 mg daily. Patients receiving greater than 100 mg daily had a hazard ratio of 7.18. Of note, patients treated for acute pain demonstrated similar outcomes. Similarly, a large case-control study of patients receiving opioids for nonmalignant pain determined odds ratio of death for patients taking 50–99 mg/d of morphine equivalents, compared to be those taking <20 mg, to be 1.92 [17]. Taken together, these data support the observation that higher opioid daily doses are associated with increased risk of mortality, even in the presence of tolerance.

The risk of drug-related overdose increases with increased opioid dosing, and there is no threshold dividing “safe” from “toxic” dosing. It is the position of ACMT that providers always exercise caution when prescribing outpatient opioids, especially in doses that exceed 50 mg daily (in morphine equivalents), due to the increased risk for drug-related overdose or death.

C. Tamper-Resistant and Abuse-Deterrent Opioid Formulations

Tamper-resistant and abuse-deterrent formulations of opioid have been employed to decrease misuse by the non-oral route, such as intravenous injection or nasal insufflation. Types of deterrents include physical/chemical barriers, co-formulation with opioid antagonists, drug release designs, new molecular entities and prodrugs, and aversive additives [18, 19]. Physical barriers are materials that limit the ability to crush or inject tablets. Opioid antagonist combination formulations consist of an opioid antagonist in a sequestered form that is not systemically available unless the product is tampered or taken by a route other than indicated. Drug release designs include sustained-release depot injectable formulations or subcutaneous implants that are difficult to manipulate. New molecular entities and prodrugs include entities that require enzymatic activation, provide different receptor binding profiles, or achieve slower central nervous system penetration. Aversive additives create an unpleasant sensation if the product is insufflated.

OxyContin™ (oxycodone hydrochloride) was reformulated in 2010 to complicate tablet tampering. Following clinical trials, FDA permitted an abuse-deterrent designation on the label. After the introduction of the new formulation, surveys indicating past month misuse decreased from 45.1 to 26.0 % [20]. In subsequent months, misuse remained between 25 and 30 %. This residual abuse involved defeating the abuse-deterrent mechanism, misusing the drug in oral

form, and shifting to other opioid formulations, including heroin [21]. Other opioids such as Hysingla™ ER (hydrocodone bitartrate) have been granted the abuse-deterrence designation by demonstrating a decrease in "drug liking," a purported measure of abuse potential [22].

ACMT supports the development of tamper-resistant and abuse-deterrent formulations as part of a comprehensive program to decrease opioid misuse. However, deterrence of abuse does not equate to full prevention of abuse. ACMT recognizes that abuse-deterrent formulations may have a limited impact on addiction and death, because in most cases, substance misuse involves oral administration of the intact drug and injection accounts for a small percentage of misuse. In addition, the impact on non-oral misuse will be limited because users may defeat the abuse-deterrent or tamper-resistant mechanism or shift to other legal or illicit opioid formulations, such as heroin [23].

Acknowledgements ACMT would like to acknowledge Members of the Position Statement and Guidelines Committee for authorship of this statement: Andrew Stolbach (Chair), Jeffrey Brent, Peter Chase, Howard Greller, Ronald Kirschner, Charles McKay, Thomas Kurt, Lewis Nelson, Sean Rhyee, Silas Smith, Brandon Warrick.

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